Update and approach to patients with brain abscess

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Purpose of review
The epidemiology of brain abscess has changed in recent decades. Moreover, acute and long-term management remains challenging with high risks of mortality and neurological sequelae. This review describes recent advances in epidemiology, diagnosis, and treatment of brain abscess.

Recent findings
The incidence of brain abscess is increasing, especially among elderly individuals. Important predisposing conditions include dental and ear-nose-throat infections, immuno-compromise, and previous neurosurgery. Molecular-based diagnostics have improved our understanding of the involved microorganisms and oral cavity bacteria including anaerobes are the predominant pathogens. The diagnosis relies upon a combination of magnetic resonance imaging, neurosurgical aspiration or excision, and careful microbiological examinations. Local source control by aspiration or excision of brain abscess combined with long-term antimicrobials are cornerstones of treatment. Long-term management remains important and should address neurological deficits including epilepsy, timely diagnosis and management of comorbidities, and potential affective disorders.

Summary
A multidisciplinary approach to acute and long-term management of brain abscess remains crucial and source control of brain abscess by neurosurgery should be pursued whenever possible. Numerous aspects regarding diagnosis and treatment need clarification. Nonetheless, our understanding of this complicated infection is rapidly evolving.

Keywords
brain abscess, cerebral abscess, diagnosis, management, treatment

INTRODUCTION

Brain abscess is a life-threatening infection that is defined as an encapsulated area of pus within the brain parenchyma [1]. Although it is an uncommon disease, the incidence is increasing and there are numerous potential causative pathogens that range from bacteria including branch-forming bacteria to fungi and parasites [2,3▪,4]. Brain abscess is usually first identified by magnetic resonance imaging (MRI) and subsequently confirmed by neurosurgical aspiration of pus in patients with e.g. headache during a couple of weeks, a new-onset neurological deficit, or seizures at time of diagnosis. Furthermore, some patients present with or develop rupture of brain abscess during admission [3▪,5–7]. This results in fulminant meningitis and is associated with a high risk of poor outcome.

Management of brain abscess is challenging and is usually a multidisciplinary endeavor involving infectious diseases specialists, neurosurgeons, neurologists, and clinical microbiologists. Cornerstones of treatment comprise both local source control by neurosurgical aspiration or excision and prolonged antimicrobial treatment through 6–8 weeks [1,8▪,9]. The risk of fatal outcome during treatment is 5–7% and increases to approximately 20% at one year after diagnosis [2,10▪,11]. In addition, survivors of brain abscess often experience significant neurological deficits that may substantially impair their work capability as well as quality of life [3▪,4,11,12▪].

A guideline on diagnosis and management of brain abscess was published on behalf of the

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KEY POINTS

- The overall incidence of brain abscess is increasing, especially among elderly individuals.
- Dental infections, immuno-compromise, ear-nose-throat infections, and previous neurosurgery appear to be important risk factors.
- Oral cavity bacteria are the most frequent pathogens and brain abscesses caused by these pathogens are almost always polymicrobial.
- Neurosurgical aspiration or excision is pivotal to confirm the diagnosis, identify the pathogen, and establish local source control.
- Targeted antimicrobials should be used for 6–8 weeks, whereas the safety of early switch to oral antimicrobials remains to be determined.

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in 2023 [8▪]. Still, the limited number of high-quality studies precluded a robust evidence base for several recommendations on important clinical dilemmas. This emphasizes the need for intensified collaborative efforts among clinicians to further strengthen a multidisciplinary approach with subsequent regular evaluations of effect on patient care. Here, an update on the epidemiology and outline for diagnosis and treatment of brain abscess is provided with further discussion of contemporary controversies in management (Figs. 1 and 2).

DEVELOPMENTS IN EPIDEMIOLOGY

The age demographics of patients with brain abscess relies somewhat on the relative prevalence of predisposing conditions and has changed through the decades. Historically, brain abscess often occurred in young adult males following head trauma due to acts of violence or traffic or work-related accidents [13,14▪,15–18]. Other important predisposing conditions were chronic ear infections, sinusitis, and vascular right-to-left shunting of transient bacteremia in children with cyanotic congenital heart disease [19,20]. Although these risk factors remain common in certain parts of the world, brain abscess is becoming less frequent in children due to prenatal diagnostics of congenital heart disease and advances in corrective surgery as well as improvements in management of chronic ear infections [2,20]. On the other hand, the overall incidence of brain abscess seems to be increasing, especially in elderly

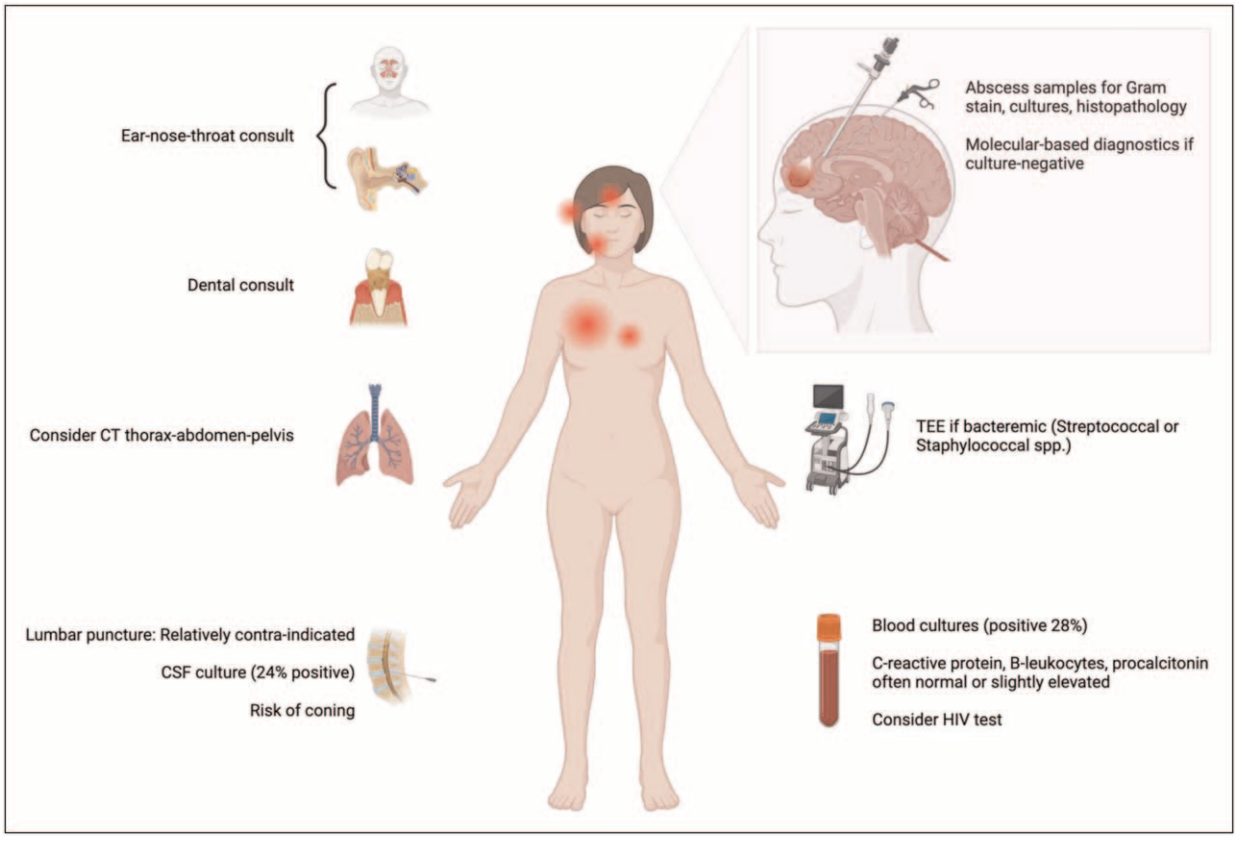
Ear-nose-throat consult
Dental consult
Consider CT thorax-abdomen-pelvis
Lumbar puncture: Relatively contra-indicated
CSF culture (24% positive)
Risk of coning
Abscess samples for Gram stain, cultures, histopathology
Molecular-based diagnostics if culture-negative
TEE if bacteremic (Streptococcal or Staphylococcal spp.)
Blood cultures (positive 28%)
C-reactive protein, B-leukocytes, procalcitonin often normal or slightly elevated
Consider HIV test

FIGURE 1. Approach to diagnostic work-up in a patient with suspected brain abscess. ∗Created with biorender.com.

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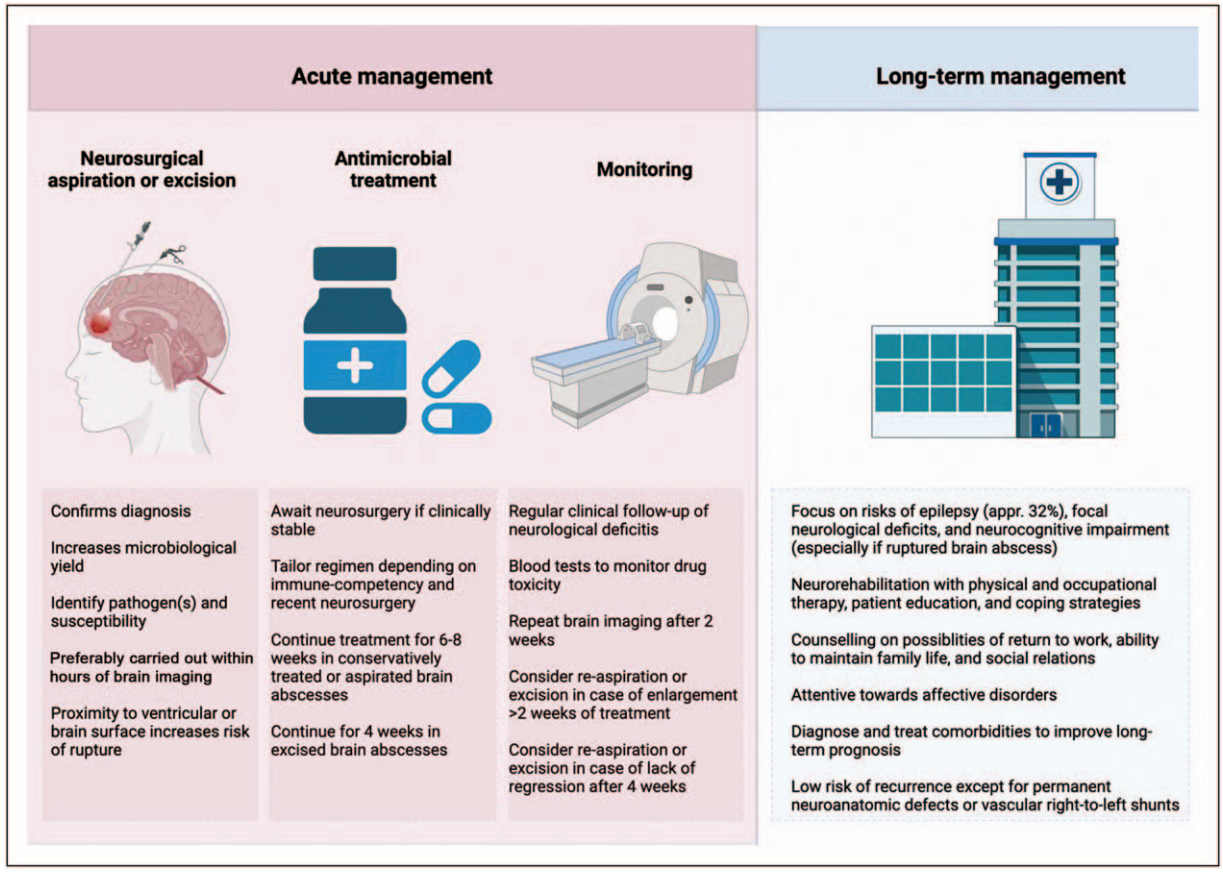
Acute management
Long-term management
Neurosurgical aspiration or excision
Antimicrobial treatment
Monitoring
Confirms diagnosis
Increases microbiological yield
Identify pathogen(s) and susceptibility
Preferably carried out within hours of brain imaging
Proximity to ventricular or brain surface increases risk of rupture
Await neurosurgery if clinically stable
Tailor regimen depending on immune-competency and recent neurosurgery
Continue treatment for 6-8 weeks in conservatively treated or aspirated brain abscesses
Continue for 4 weeks in excised brain abscesses
Regular clinical follow-up of neurological deficitis
Blood tests to monitor drug toxicity
Repeat brain imaging after 2 weeks
Consider re-aspiration or excision in case of enlargement >2 weeks of treatment
Consider re-aspiration or excision in case of lack of regression after 4 weeks
Focus on risks of epilepsy (appr. 32%), focal neurological deficits, and neurocognitive impairment (especially if ruptured brain abscess)
Neurorehabilitation with physical and occupational therapy, patient education, and coping strategies
Counselling on possiblities of return to work, ability to maintain family life, and social relations
Attentive towards affective disorders
Diagnose and treat comorbidities to improve long-term prognosis
Low risk of recurrence except for permanent neuroanatomic defects or vascular right-to-left shunts

FIGURE 2. Management of patients with brain abscess. ∗Created with biorender.com.

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populations [2,10▪]. This may be partially based on increased availability and lower thresholds for use of brain imaging, which continues to improve in resolution and quality. Other contributing factors may be increased use of immuno-modulating treatments and advanced neurosurgical procedures with associated risks of infection. Odontogenic infections were frequently reported as a major risk factor for brain abscess in recent studies [3▪,21,22▪,23▪]. Still, a large population-based case-control study found no association between number of dentist consultations or invasive dental procedures and risk of brain abscess [24▪]. Since periodontitis is prevalent in approximately 50% of the adult population, this suggests that continuous exposure to impaired anatomical barriers in the oral cavity may contribute relatively more to risk of brain abscess compared with single higher-exposure events such as invasive dental procedures [24▪,25]. Several recent studies have focused on the high absolute and relative risk of developing brain abscess in patients with Hereditary Hemorrhagic Telangiectasia (HHT) and associated pulmonary arteriovenous malformations (PAVM) if left untreated [26,27▪,28]. A case-control study accessed a US-based national claims database and confirmed previous results of a significantly increased risk in adults with HHT [27▪]. Although the overall prevalence of HHT was low in cohort studies of patients with brain abscess, it should be considered in patients with recurrent brain abscess [29–31]. Interestingly, males remain at increased risk of brain abscess compared with females (ratio 2 : 1) for unclear reasons [2,4].

The etiology of brain abscess is heterogenous as previously mentioned. Still, the relative frequency of causative pathogens is consistent across continents with oral cavity bacteria (e.g. various combinations of *Streptococcus anginosus* group, *Aggregatibacter* spp., *Fusobacterium* spp., and *Actinomyces* spp.) as the most predominant culprits followed by *Staphylococcus aureus* with some minor variations in recent studies (Table 1) [3▪,4,23▪,32–35]. Fungi and nocardiosis are common causes of brain abscess in patients with hematological malignancies and solid organ transplant recipients, whereas toxoplasmosis is frequent in patients with AIDS [3▪,8▪,36–40]. An important caveat is that *Mycobacterium tuberculosis* is likely reported separately in studies from highly endemic areas which may skew the relative pathogen distribution in such areas. Secular variations in Group A

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Table 1. Distribution of identified pathogens in patients with brain abscess in selected recent studies

First author, year	Study characteristics				Pathogens n/N (%)				
	Country	Design	Study period	Study population	Oral cavity bacteria[a]	*S. aureus*	Enterobacterales	Opportunistic[b]	Other or unknown
Bodilsen, 2022 [3▪]	Denmark	Nationwide, population-based multicenter, bi-directional	2007–2020	485 (adults)	287 (59)	27 (6)	16 (3)	45 (10)	39 (8)
Darlow, 2020 [32]	England	Single-center retrospective cohort	2013–2016	47 (adults, bacterial)	32 (68)	1 (2)	4 (9)	2 (4)	8 (17)
Makwana, 2021 [34]	Wales	Single-center retrospective cohort	2008–2018	25 (children, community-acquired)	15 (60)	2 (8)	–	–	8 (32)
Evans, 2022 [33]	England	Single-center retrospective cohort	2018–2020	29	19 (66)	–	3 (10)	2 (7)	5 (17)
Hirata, 2022 [35]	Japan	Single-center retrospective cohort	2008–2021	25 (adults, community-acquired)	11 (44)	–	–	–	14 (56)
Kameda-Smith, 2022 [87]	Canada	Single-center retrospective cohort	2009–2019	139	58 (42)	11 (8)	9 (6)	9 (6)	52 (37)
Andersen, 2022 [48▪▪]	Denmark	Single-center retrospective cohort	2011–2017	41 (spontaneous)	26 (55)	1 (2)	2 (4)	7 (17)	5 (12)
Gora, 2022 [14▪]	Australia	Single-center retrospective cohort	2000–2019	84	12 (14)	6 (7)	5 (6)	10 (12)	51 (61)
Boukobza, 2023 [88]	France	Single-center prospective cohort of endocarditis	2005–2020	20 (endocarditis)	5 (25)	9 (45)	–	1 (5)	5 (25)
Roy, 2023 [22▪]	England	Single-center retrospective cohort	2002–2018	87	59 (68)	10 (11)	3 (3)	1 (1)	14 (16)

Patients with brain abscess due to oral cavity bacteria were assumed to be polymicrobial and were grouped together, whereas other pathogens were assumed to be monomicrobial.
S. aureus. *Staphylococcus aureus*.
[a]Oral cavity bacteria were defined as *Streptococcus* spp., *Hemophilus* spp., *Actinomyces* spp., *Peptostreptococcus* spp., and *Fusobacterium* spp.
[b]Opportunitis pathogens were defined as *Nocardia* spp., *Listeria monocytogenes*, parasites, and fungi whenever specified.

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streptococcal (GAS) epidemiology combined with normalization of societal restrictions after COVID-19 caused a relative surge of invasive GAS infections including bacterial meningitis and intracranial empyema [41–43]. Still, the absolute risk of invasive GAS infections is low and brain abscess caused by this pathogen remains very rare [44].

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USE OF MOLECULAR-BASED DIAGNOSTICS

Several studies have examined the added diagnostic yield of molecular-based diagnostics compared with standard cultures in samples of pus from patients with brain abscess. Although the studies varied in methodology, the findings of molecular-based diagnostics were concordant with culture results in approximately 70% of cases [8▪]. They also consistently expanded the number of identified microorganisms (usually anaerobic bacteria) in samples from patients with brain abscess due to oral cavity bacteria detected by culture [8▪,45–47]. Importantly, the clinical relevance of such results was substantiated by a carefully conducted study that was able to grow fastidious microorganisms from frozen aspirates of patients with brain abscess in whom the cultured pathogens had otherwise only been identified by molecular-based diagnostics during daily clinical practice [48▪▪]. Thus, once an oral cavity bacterium has been found in brain abscess material, the patient should be managed as having a polymicrobial infection by continued treatment with a 3rd-generation cephalosporin and metronidazole. In contrast, brain abscesses caused by *S. aureus* and other pathogens have rarely been shown to be polymicrobial.

Molecular-based diagnostics have enhanced our understanding of brain abscess and may at times qualify antimicrobial treatment strategies. Still, further studies documenting a more direct clinical benefit in management of patients with brain abscess by e.g. decreased time to appropriate antimicrobial therapy, faster de-escalation of broad-spectrum antimicrobials, shortened duration of hospitalization, or an improved outcome are warranted.

IMAGING

MRI with diffusion weighted imaging and attenuated diffusion constant is the preferred radiological examination in patients with ring-enhancing lesions with a positive predictive value of 88% and a negative predictive value of 90% for brain abscess [8▪]. Diagnosis of cerebritis remains challenging but may present as poorly demarcated hyperintense lesions on FLAIR/T2-weighted images combined with absent to mild contrast enhancement on T1-weighted images [49]. Among other radiological modalities, a recent single-center prospective observational cohort study showed that MR spectroscopy was not helpful for differentiating brain abscess from tumor in patients already treated with antibiotics for >72 h [50].

NEUROSURGICAL ASPIRATION OR EXCISION

The neurosurgical approach to treatment of brain abscess may differ substantially from surgeon to surgeon and hospital to hospital [3▪,8▪,33,34,51▪,52▪]. A diameter above 2 or 2.5 cm is often referenced as a rule of thumb to carry out aspiration or excision of brain abscess although stereo-tactic navigation allows for accurate targeting of abscesses as small as 1 cm in diameter [51▪]. It appears that this pragmatic and somewhat arbitrary threshold has been broadly adopted after discussion in publications by an influential group of neurosurgeons in the 1980s and 1990s without specific data demonstrating an association between abscess size and neurosurgical or overall outcome [53–55].

A neurosurgical intervention is pivotal in management of patients with brain abscess for several reasons. Since brain abscess is mistaken for tumor on MRI in approx. 10% of cases, aspiration or excision allows confirmation of the diagnosis by obtainment of pus and is additionally crucial for ensuring local source control of the infection within the brain. This is also in alignment with algorithms for treatment of abscesses elsewhere in the body. In addition, it enables pathogen identification and susceptibility testing for rational and targeted antibiotics during the ensuing 6–8 weeks, where switches in treatment are often required due to development of toxicity or convenience. Some individuals may be managed without neurosurgery but this strategy has been associated with treatment failure and increased mortality in several studies and there are currently no robust predictors of rupture, death, and other unfavorable outcomes in this patient population to identify those that might safely be treated using this approach [3▪,56,57,58▪]. Thus, aspiration or excision is recommended in all patients with brain abscess whenever feasible.

Aspiration of brain abscess is the preferred neurosurgical procedure in most settings due to its less invasive nature with lower risks of hemorrhage compared with excision [8▪,35,52▪,59]. However, re-aspiration or secondary excision is required in approx. 20% of cases [8▪]. Analyses of outcome according to aspiration or excision are heavily confounded by differences in study periods and populations as well

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as accessibility of the brain abscess [51▪,52▪,60]. Excision should be prioritized in fungal brain abscess and may be considered in other (recurrent) abscesses located superficially in noneloquent areas or in the cerebellum [8▪,51▪,61,62].

ANTIBIOTICS

Antimicrobial treatment may be withheld until aspiration or excision in clinically stable patients without e.g. impending rupture or herniation if neurosurgery can be carried out within reasonable time, preferably within 24 h after diagnosis [3▪,8▪]. Delayed initiation of antimicrobial treatment until after neurosurgery is associated with a significant increase in the microbiological yield of the abscess material and may thereby inform and optimize antimicrobial treatment [63,64].

Important parameters for selection of empiric antimicrobial treatment of brain abscess include pathogen distributions, pharmacokinetic aspects of the drugs, and previous experiences for central nervous system (CNS) infections. The ESCMID guidelines for treatment of brain abscess recommend a third-generation cephalosporin combined with metronidazole for empiric treatment of community-acquired brain abscess with the addition of voriconazole and trimethoprim-sulfamethoxazole in solid organ transplant recipients and in patients with hematological malignancies or serious immune-modulating treatments (Table 2) [8▪].

Duration of treatment remains poorly defined and is currently recommended to comprise 6–8 weeks of intravenous antimicrobials for aspirated or conservatively treated patients and 4 weeks in patients with excised brain abscess [8▪]. A few observational studies with no or only historical comparison cohorts suggest that treatment duration may be successfully shortened to 3–4 weeks if combined with abscess irrigation, drainage, or intracavitary antibiotic instillation [64,65]. However, this strategy cannot be recommended at present and needs to be confirmed in other studies with carefully selected control groups and prolonged follow-up.

Oral consolidation treatment after a full course of 6–8 weeks of i.v. antibiotics has not been shown to be associated with reduced risks of relapses, recurrences, or survival and is usually restricted to difficult-to-treat opportunistic microorganisms [8▪]. Early switch to oral antibiotics is a compelling concept that has garnered a lot of attention for almost all infectious diseases during the last decades [66]. In brain abscess, this has been defined as switch to oral antimicrobials after 1–2 weeks of i.v. treatment and was first formally introduced in year 2000 in a position paper by the 'Infection in Neurosurgery' working party of the British Society for Antimicrobial Chemotherapy [67,68]. Since then, several retrospective cohort studies report successful outcomes of early switch to oral antimicrobials in selected study populations of patients with less severe disease [69–72,73▪,74▪]. To account for the inherent risks of bias in such studies, an ongoing randomized non-inferiority trial of early switch to orals antimicrobials after 2 weeks of i.v. treatment compared with continued i.v. treatment will hopefully be able to address this question in the coming years [75].

MONITORING

Monitoring of brain abscess is challenging and should primarily rely on clinical assessment. The role of repeated imaging needs to balance timely detection of potential clinically silent progression of disease with risks of radiological findings without a true clinical benefit for the patient. The latter may result in unsubstantiated prolongation of antimicrobial treatment due to delayed normalization on brain imaging. Moreover, rational use of healthcare resources should be considered as well as potential radiation exposure if computed tomography (CT) is used for monitoring. Studies comparing the radiological evolvement of patients with treatment failure and success, respectively, are sparse and restricted by limited sample sizes as well as variable follow-up [76–82]. Still, they consistently show that it is not unusual for the abscess volume to remain largely unchanged after 2 weeks of treatment, whereas progression thereafter or lack of regression after 4 weeks should trigger concern about adequate source control of the brain abscess. Contrast enhancement may persist for 3–6 months or even longer.

Consequently, follow-up imaging (CT or MRI) for brain abscess is recommended at 2 weeks post-surgery. In case of progression of abscess volume at 2 weeks after neurosurgical aspiration, a repeat aspiration or secondary excision should be carefully discussed with the patient [8▪]. The clinical relevance of brain imaging at end of treatment is unclear and is not recommended in patients who are otherwise recovering. Blood tests are rarely helpful for monitoring of brain abscess but should be carried out regularly to check drug tolerance during prolonged antimicrobial treatment and may be combined with a focused evaluation of neurological deficits and/or other infectious foci.

COMPLICATIONS AMONG SURVIVORS AND LONG-TERM FOLLOW-UP

Brain abscess may have a detrimental influence on both the immediate and long-term health of

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Table 2. Recommended antimicrobial regimens and treatment duration for brain abscess according to patient characteristics and neurosurgical approach

Type of patient	Antimicrobial treatment		Duration of treatment	
	Standard	Alternative	Neurosurgical approach	Weeks
Community-acquired brain abscess	3rd generation cephalosporin and metronidazole	Meropenem	Aspiration or conservative	6–8
			Excision	4
Severely immune-compromised patients	Add TMP-SMX and voriconazole	Meropenem combined with voriconazole and TMP-SMX	Aspiration or conservative	6–8
			Excision	4
Postneurosurgical brain abscess	Antipseudomonal cephalosporin and linezolid	Meropenem and vancomycin	Aspiration or conservative	6–8
			Excision	4

TMP-SMX, trimethoprim-sulfamethoxazole.

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individuals. Neurological deficits are present in approximately 70% of survivors of brain abscess [4]. Prognostic factors for an unfavorable outcome assessed by a Glasgow Outcome Scale score of 1–4 at 6 months after discharge include intraventricular rupture, immune-compromise, age >65 years, and female sex [3▪,4]. The long-term cumulative incidence of epilepsy is 32% with a substantially increased risk among patients with frontal lobe abscess, seizures during admission for brain abscess, aspirated or excised brain abscess, previous neurosurgery before hospitalization for brain abscess, alcohol abuse, and previous stroke [20,57,83,84]. Epilepsy was also shown to be an independent risk factor for mortality in adjusted analysis among survivors of brain abscess [83]. Individuals with a previous brain abscess have an increased risk of cancer, disability pension, and death compared with matched population controls for several years after treatment [12▪,20,57,85▪]. Survivors also have an increased use of antidepressants and anxiolytics as a proxy for affective disorders [86▪].

All these findings combined highlight the requirement and potential benefits of a continued multidisciplinary approach to patient care that extends beyond immediate management of the brain abscess. Neurorehabilitation is an essential part of this with a focus on patient education, coping strategies, and possibilities for return to work and daily activities. In addition, diagnosis and management of epilepsy and other comorbidities that may occur should be actively pursued along with attention towards affective disorders and enforcing a healthy lifestyle.

CONCLUSION

Brain abscess is a challenging and potentially fatal disease with a high risk of serious neurological complications. The predisposing conditions have changed during recent decades, but oral cavity bacteria remain the most frequent causative pathogens. Treatment is complex and requires a combination of timely source control by neurosurgery and prolonged antimicrobials in a multidisciplinary approach. Management of subsequent sequelae and comorbidities may be important areas of intervention to improve the long-term prognosis.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

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